Monatshefte für Chemie 125, 509–513 (1994)

Monatshefte für Chemie
Chemical Monthly

Determination of Nisoldipine in Film Tablets by Differential Pulse Polarography

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Summary. A differential pulse polarographic (*DPP*) method was developed for the determination of nisoldipine in Baymycard® film tablets without interference from excipients. Nisoldipine is reduced at the dropping mercury electrode in a single, irreversible peak. Linearity between the nisoldipine concentration and the peak height was observed in the $5 \cdot 10^{-4}$–10^{-7} *M* concentration range. The detection limit is 22 ng/ml. The analysis of a series of 10 Baymycard® 5 mg film tablets showed a standard deviation of ± 0.115 mg and a S_{rel} of $\pm 2.30\%$, respectively.

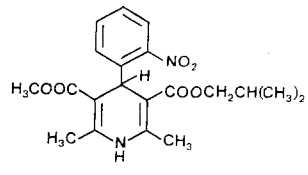
Keywords. Nisoldipine; polarography; DPP.

Gehaltsbestimmung von Nisoldipin in Filmtabletten mittels differentieller Pulspolarographie

Zusammenfassung. Eine Bestimmung von Nisoldipin in Baymycard® Filmtabletten mittels differentieller Pulspolarographie (*DPP*) wurde entwickelt, die keine Störungen durch Tablettenhilfsstoffe aufweist. Nisoldipin wird an der tropfenden Quecksilberelektrode in einem einzigen, irreversiblen Peak reduziert. Linearität zwischen Nisoldipinkonzentration und Peakhöhe wurde im Konzentrationsbereich von $5 \cdot 10^{-4}$–10^{-7} *M* festgestellt. Die Bestimmungsgrenze beträgt 22 ng/ml. Die Analyse einer Serie von 10 Baymycard® 5 mg Filmtabletten ergab eine Standardabweichung von ± 0.115 mg, dies entspricht einer S_{rel} von $\pm 2.30\%$.

Introduction

Nisoldipine, isobutylmethyl-1,4-dihydro-2,6-dimethyl-4-(2′-nitrophenyl)-pyridine-3,5-dicarboxylate, is an excellent calcium channel blocker for the cardiac muscle [1] and the smooth muscular system. According to this mode of effect, nisoldipine is used in the treatment of angina pectoris [2, 3] and hypertension [4, 5]. Only a few methods for the determination of nisoldipine have been published. They are based on gas chromatography [6], thin-layer chromatography [7] and reversed-phase liquid chromatography [8].



This study presents a differential pulse polarographic (*DPP*) method for the determination of nisoldipine in tablet formulation (5 mg Baymycard® film tablets) without interference from excipients. The DPP analysis of nisoldipine does not necessitate extraction or filtration steps and therefore it is precise, accurate and not very time-consuming especially for use in quality control. Nisoldipine shows photoinstability, especially in solutions. A study dealing with degradation products will be published separately.

Experimental

Apparatus

A polarographic analyzer model 264 A (EG&G, PARC, New Jersey/USA) equipped with a stand model 303 A SMDE (EG&G, PARC) was used in combination with a three-electrode polarographic cell (a dropping mercury working electrode, an Ag/AgCl reference electrode and a Pt wire auxiliary electrode). For preparing a calibration graph and analyzing tablets, the polarographic analyzer system was operated under the following parameters: mode, DPP; drop size, M; drop time, 1 s; potential range, −0.4 to −0.8 V; scan rate, 10 mV/s; current sensitivity, 1 uA; pulse amplitude, 50 mV.

Cyclic voltammetric measurements at the hanging mercury drop electrode were performed with the same polarographic unit.

In addition to the use of a traditional X–Y recorder, the obtained data were evaluated using computer software from ACE (Heidelberg, BRD).

All glass material was treated with conc. nitric acid for 24 hours for purification, rinsed carefully with double distilled water and dried at 40 °C.

Reagents

Both pure nisoldipine and Baymycard® film tablets were kindly made available by Bayer AG (Wuppertal, BRD). All reagents were of Suprapur® grade (E. Merck, Darmstadt, BRD) and water was of nanopure quality stored in Nalgene® containers.

Nisoldipine Standard I Solution: Transfer 50.0 mg pure nisoldipine to a 50 ml volumetric flask (painted black), dissolve in ethanol and bring to volume. Store solution in a dark, cool place. This solution contains 1 mg nisoldipine/ml and is stable for about one week.

Nisoldipine Standard II Solution: Dilute standard I solution 1:10 (v/v) with ethanol. This solution should be freshly prepared once a day (100 µg/ml).

Nisoldipine Standard III Solution: Dilute standard I solution 1:100 (v/v) with ethanol immediately before the electrochemical measurements (10 µg/ml).

McIlvaine buffer/ethanol Solution: Dissolve 11.622 g citric acid monohydrate and 9.851 g Na_2HPO_4 in 900 ml water and add 100 ml ethanol (*pH* 4.00).

Nitrogen: 99.9995% pure.

Calibration Graph

Transfer 15 ml buffer/ethanol solution to a black painted polarographic cell and purge for deoxygenation with nitrogen for 8 min. Add a series of 50–500 µl nisoldipine standard II solution and purge for another 30 s, prior to recording the series of polarograms using the previously described instrumental parameters. Measure the peak heights using the tangents method with reference to the blank solution polarogram and consider the increase of volume. A concentration range of 5–50 µg/15 ml is obtained.

Tablet Analysis Procedure

Put one 5 mg film tablet into a 50 ml black painted volumetric flask, and 5 ml buffer/ethanol solution and let stir for 1 min on a magnetic stirrer. After pippeting 20 ml ethanol to the flask, continue stirring for further 10 min. Add 15 ml buffer/ethanol solution and bring to volume with ethanol while rinsing and removing the magnetic stick. Follow the procedure described under *Calibration Graph* by pipetting 100 µl of the tablet suspension (instead of nisoldipine standard II solution) to the cell and record the polarogram. Apply the standard addition method by adding 3 times 100 µl each of nisoldipine standard II solution to the polarographic cell. Record the polarograms and evaluate the data.

Results and Discussion

Polarographic Behavior of Nisoldipine

In order to obtain information on the nature of the electrode reaction as well as data for the proper analytical conditions, the *pH* dependence was investigated using both differential pulse polarography (*DPP*) and cyclic voltammetry (*CV*). *Britton-Robinson* buffer and/or *McIlvaine* buffer were used as supporting electrolytes (*pH* range 2.2–10.0) in a mixture with 10% ethanol as a solubilizer [9]. Nisoldipine showed a single, well formed DPP reduction peak and only one cathodic wave using the CV mode (Fig. 1). Therefore, the electrode reaction is assumed to be irreversible and must be attributed to the reduction of the nitro group to the hydroxylamine derivative [10–12].

$$R\text{–}NO_2 + 4H^+ + 4e^- \rightarrow R\text{–}NHOH + H_2O$$

Since the protons are involved in the electrode reaction, a typical shift of the peak potential (E_p) to more negative values was expected when the DPP mode was applied. An ΔE value of $-0.58\,mV/pH$ was obtained in the *pH* range of 4.1–8.3 (Fig. 2).

On the other hand, the peak heights at the same nisoldipine concentration were not essentially dependent upon the H^+ concentration. Of interest to analytical application was the fact that the *McIlvaine* buffer system showed the highest sensitivity in the *pH* range 2.5–5.0.

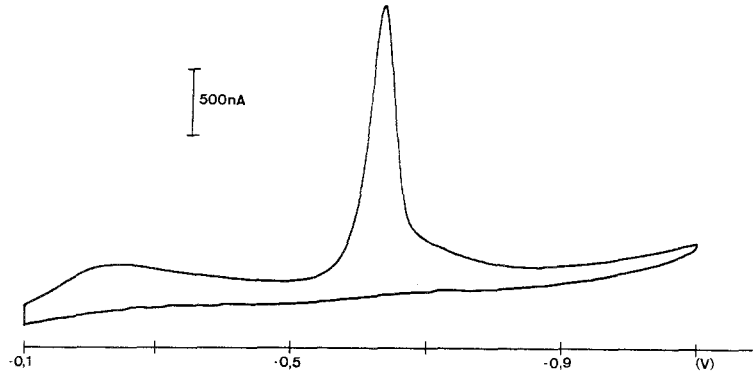


Fig. 1. Cyclic voltammogramm of $10^{-4}\,M$ nisoldipine in *McIlvaine* buffer *pH* 4.0/10% ethanol solution; scan rate: 100 mV/s

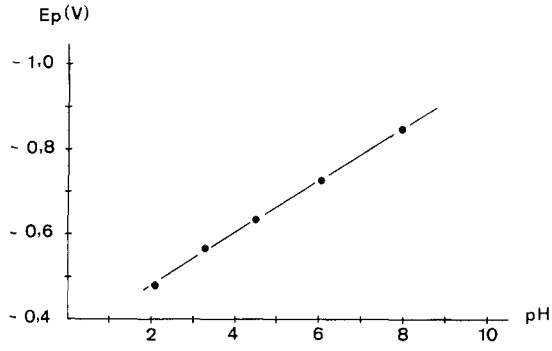


Fig. 2. Dependence of electrode potential upon *pH*

Determination of Nisoldipine by DPP

In order to develop a reliable and reproducible method for the determination of nisoldipine especially in tablet formulations, the analytical conditions had to be optimized resulting in the recommended working procedures. The well-defined, diffusion-controlled, irreversible reduction peaks showed a strict linearity of peak heights versus concentration of nisoldipine within a wide range (Fig. 3). By using nisoldipine standard I–III solutions and adapting the current sensitivity, nisoldipine can be determined in the concentration range of 40 ng to 200 µg/ml (10^{-7}–$5 \cdot 10^{-4}$ *M*). The detection limit was found to be 22 ng/ml.

An estimate of precision, obtainable by the recommended procedure, was made by means of linear regression analysis. In the 0.4–4 µg/ml concentration range it gave an intercept of almost 0, a correlation coefficient of 0.9998 and a standard deviation (S_k) of $\pm$ 7.6 ng/ml (according to [13]). The S_k value leads to a relative standard deviation (S_{rel}) of $\pm$ 1.14% at the concentration of nisoldipine (0.67 µg/ml) which is equivalent to a 5 mg tablet.

Assay of Nisoldipine in Baymycard® Film Tablets

To eliminate the inconstancy of weight, 20 Baymycard® tablets out of several packages were weighed and finely pulverized. The average weight of one tablet was 135.2 mg. Ten portions of 135.2 mg each were analyzed employing the described

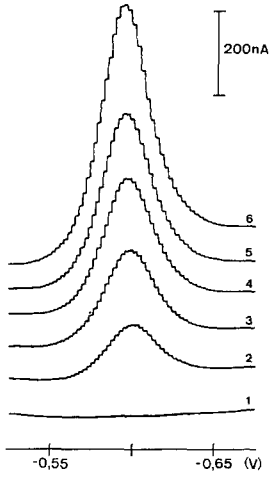


Fig. 3. Differential pulse polarograms of nisoldipine in *McIlvaine* buffer *pH* 4.0/10% ethanol solutions. (1) 0, (2) 0.60, (3) 1.10, (4) 1.60, (5) 2.10, (6) 3.10 µg/ml. The plots are displaced and evaluated applying the tangents method

Table 1. Determination of nisoldipine in 5 mg Baymycard® film tablets

No.	Weight of tablet (mg)	Nisoldipine (mg)
1	134.3	5.05
2	138.2	4.74
3	132.8	5.02
4	135.2	4.97
5	137.6	4.91
6	136.2	5.09
7	135.4	4.96
8	133.8	4.97
9	135.7	5.03
10	132.7	5.17
	$\bar{X} = 135.2$	$\bar{X} = 4.99$
	$S = \pm 1.85$	$S = \pm 0.115$
	$S_{rel} = \pm 1.37\%$	$S_{rel} = \pm 2.30\%$

procedure. The analysis gave a mean value of 4.99 ± 0.092 mg nisoldipine, or a S_{rel} value of $\pm 1.84\%$.

The results of the determination of nisoldipine in different Baymycard® 5 mg tablets are listed in Table 1.

The proposed differential pulse polarographic method for the determination of nisoldipine is an accurate, sensitive and efficient one, even in the presence of tablet matrix. The time required for one determination is about 15 min.

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Received August 26, 1993. Accepted October 7, 1993